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 NEWS  1          Web Page for STN Seminar Schedule - N. America
 NEWS  2  OCT 02  CA/CAplus enhanced with pre-1907 records from Chemisches
                  Zentralblatt
 NEWS  3  OCT 19  BEILSTEIN updated with new compounds
 NEWS  4  NOV 15  Derwent Indian patent publication number format enhanced
 NEWS  5  NOV 19  WPIX enhanced with XML display format
 NEWS  6  NOV 30  ICSD reloaded with enhancements
 NEWS  7  DEC 04  LINPADOCDB now available on STN
 NEWS  8  DEC 14  BEILSTEIN pricing structure to change
 NEWS  9  DEC 17  USPATOLD added to additional database clusters
 NEWS 10  DEC 17  IMSDRUGCONF removed from database clusters and STN
 NEWS 11  DEC 17  DGENE now includes more than 10 million sequences
 NEWS 12  DEC 17  TOXCENTER enhanced with 2008 MeSH vocabulary in
                  MEDLINE segment
 NEWS 13  DEC 17  MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
 NEWS 14  DEC 17  CA/CAplus enhanced with new custom IPC display formats
 NEWS 15  DEC 17  STN Viewer enhanced with full-text patent content
                  from USPATOLD
 NEWS 16  JAN 02  STN pricing information for 2008 now available
 NEWS 17  JAN 16  CAS patent coverage enhanced to include exemplified
                  prophetic substances
 NEWS 18  JAN 28  USPATFULL, USPAT2, and USPATOLD enhanced with new
                  custom IPC display formats
 NEWS 19  JAN 28  MARPAT searching enhanced
 NEWS 20  JAN 28  USGENE now provides USPTO sequence data within 3 days
                  of publication
 NEWS 21  JAN 28  TOXCENTER enhanced with reloaded MEDLINE segment
 NEWS 22  JAN 28  MEDLINE and LMEDLINE reloaded with enhancements
 NEWS 23  FEB 08  STN Express, Version 8.3, now available
 NEWS 24  FEB 20  PCI now available as a replacement to DPCI
 NEWS 25  FEB 25  IFIREF reloaded with enhancements
 NEWS 26  FEB 25  IMSPRODUCT reloaded with enhancements
 NEWS 27  FEB 29  WPINDEX/WPIDS/WPIX enhanced with ECLA and current
                  U.S. National Patent Classification


 NEWS EXPRESS FEBRUARY 08 CURRENT WINDOWS VERSION IS V8.3,
              AND CURRENT DISCOVER FILE IS DATED 20 FEBRUARY 2008

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FILE 'HOME' ENTERED AT 23:19:10 ON 28 MAR 2008

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
       AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
       CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
       DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 23:19:26 ON 28 MAR 2008

69 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
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=> s (transferrin or insulin)(P)substitute? and (PEG or polyethylene glycol) and
culture(p)medi?
          0*  FILE ADISNEWS
          0*  FILE ANTE
          0*  FILE AQUALINE
          0*  FILE BIOENG
         10*  FILE BIOTECHABS
         10*  FILE BIOTECHDS
          0*  FILE BIOTECHNO
  13 FILES SEARCHED...
          5   FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
  27 FILES SEARCHED...
          1   FILE EMBASE
          1*  FILE ESBIOBASE
          0*  FILE FOMAD
          0*  FILE FOREGE
          0*  FILE FROSTI
          0*  FILE FSTA
          2   FILE IFIPAT
          0*  FILE KOSMET
  42 FILES SEARCHED...
          1   FILE MEDLINE
          0*  FILE NTIS
          0*  FILE NUTRACEUT
          1*  FILE PASCAL
          0*  FILE PHARMAML
          1   FILE PHIN
  52 FILES SEARCHED...
          1   FILE SCISEARCH
        484   FILE USPATFULL
         82   FILE USPAT2
          0*  FILE WATER
  66 FILES SEARCHED...
          5   FILE WPIDS
          5   FILE WPINDEX

  14 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L1   QUE (TRANSFERRIN OR INSULIN)(P) SUBSTITUTE? AND (PEG OR POLYETHYLENE GLYCO
         L) AND CULTURE(P) MEDI?

=> file biotechabs biotechds caplus embase esbiobase ifipat medline pascal phin
scisearch uspatfull uspat2
COST IN U.S. DOLLARS                                 SINCE FILE      TOTAL
                                                          ENTRY    SESSION
FULL ESTIMATED COST                                        3.25       3.46

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FILE 'USPAT2' ENTERED AT 23:22:11 ON 28 MAR 2008
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=> s l1
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN)(P) SUBSTITUT'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'CULTURE(P) MEDI?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN)(P) SUBSTITUT'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'CULTURE(P) MEDI?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
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FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN)(P) SUBSTITUT'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'CULTURE(P) MEDI?'
   7 FILES SEARCHED...
L2          589 L1

=> s L2 and recombinant protein?
L3          132 L2 AND RECOMBINANT PROTEIN?

=> s l3 and animal protein?
L4            8 L3 AND ANIMAL PROTEIN?

=> s l3 and sodium erythorbate
L5            3 L3 AND SODIUM ERYTHORBATE

=> d l5 1-3

L5   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2004:326209  CAPLUS
DN   140:317692
TI   Animal cell culture or tissue culture media
     containing polyethylene glycol
IN   Heron, Antoine
PA   Maco Pharma, Fr.
SO   Eur. Pat. Appl., 11 pp.
     CODEN: EPXXDW
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   EP 1411115           A1    20040421    EP 2003-292374         20030926
     EP 1411115           B1    20070509
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     FR 2846004           A1    20040423    FR 2002-12878          20021016
     FR 2846004           B1    20060623
     AT 361971            T     20070615    AT 2003-292374         20030926
     AU 2003252890        A1    20040506    AU 2003-252890         20031009
     CA 2444468           A1    20040416    CA 2003-2444468        20031015
     US 2004087021        A1    20040506    US 2003-685609         20031015
     JP 2004135672        A     20040513    JP 2003-356717         20031016
PRAI FR 2002-12878        A     20021016
RE.CNT  4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 2 OF 3  IFIPAT  COPYRIGHT 2008 IFI on STN
AN    10579799  IFIPAT;IFIUDB;IFICDB
TI    COMPOSITON FOR CULTURING CELLS, IN PARTICULAR ANIMAL OR TISSUE CELLS, AND
      A CULTURE MEDIUM COMPRISIING SUCH A COMPOSITION;
      NUTRIENT BROTH COMPRISING SODIUM ERYTHORBATE FOR
      PROPAGATING EUKARYOTIC CELLS; BIOREACTORS AND HETEROLOGOUS PROTEIN
      EXPRESSION
IN    Heron Antoine (FR)
PA    Unassigned Or Assigned To Individual (68000)
PPA   Macopharma FR (Probable)
PI    US 2004087021   A1  20040506
AI    US 2003-685609      20031015
PRAI  FR 2002-12878       20021016
FI    US 2004087021       20040506
DT    Utility; Patent Application - First Publication
FS    CHEMICAL
```

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      APPLICATION
ED    Entered STN: 7 May 2004
      Last Updated on STN: 31 Oct 2005
CLMN  38

L5   ANSWER 3 OF 3  USPATFULL on STN
AN     2004:114182  USPATFULL
TI     Compositon for culturing cells, in particular animal or tissue cells,
       and a culture medium comprisiing such a composition
IN     Heron, Antoine, Halluin, FRANCE
PI     US 2004087021       A1  20040506
AI     US 2003-685609      A1  20031015 (10)
PRAI   FR 2002-12878       20021016
DT     Utility
FS     APPLICATION
LN.CNT 619
INCL   INCLM: 435/404.000
NCL    NCLM:  435/404.000
IC     [7]
       ICM    C12N005-02
       IPCI   C12N0005-02 [ICM,7]
       IPCR   C12N0005-06 [I,C*]; C12N0005-06 [I,A]; C12N0005-00 [I,C*];
              C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
              C12N0005-08 [I,C*]; C12N0005-08 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d l4 1-8

L4    ANSWER 1 OF 8  BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
AN    2004-15746  BIOTECHDS
TI    Animal protein free composition for culturing cells
      or tissues comprises polyethylene glycol as an
      albumin substitute;
          animal protein-free composition for use in tissue
        culture and gene therapy
AU    HERON A
PA    MACO PHARMA SA
PI    EP 1411115 21 Apr 2004
AI    EP 2003-292374 26 Sep 2003
PRAI  FR 2002-12878 16 Oct 2002; FR 2002-12878 16 Oct 2002
DT    Patent
LA    French

L4   ANSWER 2 OF 8  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2004:326209  CAPLUS
DN   140:317692
TI   Animal cell culture or tissue culture media
     containing polyethylene glycol
IN   Heron, Antoine
PA   Maco Pharma, Fr.
SO   Eur. Pat. Appl., 11 pp.
     CODEN: EPXXDW
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   EP 1411115           A1    20040421    EP 2003-292374         20030926
     EP 1411115           B1    20070509
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     FR 2846004          A1    20040423    FR 2002-12878          20021016
     FR 2846004          B1    20060623
     AT 361971           T     20070615    AT 2003-292374         20030926
     AU 2003252890       A1    20040506    AU 2003-252890         20031009
     CA 2444468          A1    20040416    CA 2003-2444468        20031015
     US 2004087021       A1    20040506    US 2003-685609         20031015
     JP 2004135672       A     20040513    JP 2003-356717         20031016
PRAI FR 2002-12878       A     20021016
RE.CNT  4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4   ANSWER 3 OF 8  IFIPAT  COPYRIGHT 2008 IFI on STN
AN     10579799  IFIPAT;IFIUDB;IFICDB
TI     COMPOSITON FOR CULTURING CELLS, IN PARTICULAR ANIMAL OR TISSUE CELLS, AND
       A CULTURE MEDIUM COMPRISIING SUCH A COMPOSITION;
       NUTRIENT BROTH COMPRISING SODIUM ERYTHORBATE FOR PROPAGATING EUKARYOTIC
       CELLS; BIOREACTORS AND HETEROLOGOUS PROTEIN EXPRESSION
IN     Heron Antoine (FR)
PA     Unassigned Or Assigned To Individual (68000)
PPA    Macopharma FR (Probable)
PI     US 2004087021   A1  20040506
AI     US 2003-685609      20031015
PRAI   FR 2002-12878       20021016
FI     US 2004087021       20040506
DT     Utility; Patent Application - First Publication
FS     CHEMICAL
       APPLICATION
ED     Entered STN: 7 May 2004
       Last Updated on STN: 31 Oct 2005
CLMN   38

L4   ANSWER 4 OF 8  USPATFULL on STN
AN      2007:220488  USPATFULL
TI      Method for culturing Chinese hamster ovary cells
IN      Keen, Michael J., Beckenham, UNITED KINGDOM
        Rapson, Nicholas T., Stapleford, UNITED KINGDOM
PA      SmithKline Beecham Corporation, Philadelphia, PA, UNITED STATES (U.S.
        corporation)
PI      US 39792            E1  20070821
        US 5633162              19970527 (Original)
AI      US 2004-995010          20041122 (10)
        US 1994-205379          19940304 (Original)
RLI     Continuation of Ser. No. US 1992-991717, filed on 18 Dec 1992, Pat. No.
        US 5316938 Continuation of Ser. No. US 1991-777729, filed on 16 Oct
        1991, ABANDONED
PRAI    GB 1990-22545       19901017
DT      Reissue
FS      GRANTED
LN.CNT 983
INCL    INCLM: 435/384.000
        INCLS: 435/386.000; 435/387.000; 435/325.000; 435/358.000; 435/359.000;
               435/360.000; 435/361.000; 435/383.000; 435/326.000
NCL     NCLM:  435/384.000
        NCLS:  435/325.000; 435/326.000; 435/358.000; 435/359.000; 435/360.000;
               435/361.000; 435/383.000; 435/386.000; 435/387.000
IC      IPCI   C12N0005-00 [I,A]
EXF     435/325; 435/326; 435/358; 435/359; 435/360; 435/361; 435/362; 435/383;
        435/384; 435/387; 435/386

L4   ANSWER 5 OF 8  USPATFULL on STN
AN      2006:86590  USPATFULL
TI      Cell culture media
```

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IN      Abitorabi, M. Abi, Morgan Hill, CA, UNITED STATES
        Guerini, Michael N., Ong, NE, UNITED STATES
        Taylor, Stephen A., Santa Cruz, CA, UNITED STATES
        Hernandez, Guadalupe G., San Jose, CA, UNITED STATES
        Simonsen, Christian C., Carmel, CA, UNITED STATES
PI      US 2006073591       A1  20060406
AI      US 2005-32558       A1  20050110 (11)
PRAI    US 2004-535580P     20040109 (60)
        US 2004-568084P     20040504 (60)
DT      Utility
FS      APPLICATION
LN.CNT 6174
INCL    INCLM: 435/404.000
        INCLS: 435/070.210
NCL     NCLM:  435/404.000
        NCLS:  435/070.210
IC      IPCI   C12P0021-04 [I,A]; C12N0005-00 [I,A]
        IPCR   C12P0021-04 [I,A]; C12N0005-00 [I,C]; C12N0005-00 [I,A];
               C12P0021-04 [I,C]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4   ANSWER 6 OF 8  USPATFULL on STN
AN      2004:114182  USPATFULL
TI      Compositon for culturing cells, in particular animal or tissue cells,
        and a culture medium comprisiing such a composition
IN      Heron, Antoine, Halluin, FRANCE
PI      US 2004087021       A1  20040506
AI      US 2003-685609      A1  20031015 (10)
PRAI    FR 2002-12878       20021016
DT      Utility
FS      APPLICATION
LN.CNT 619
INCL    INCLM: 435/404.000
NCL     NCLM:  435/404.000
IC      [7]
        ICM    C12N005-02
        IPCI   C12N0005-02 [ICM,7]
        IPCR   C12N0005-06 [I,C*]; C12N0005-06 [I,A]; C12N0005-00 [I,C*];
               C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
               C12N0005-08 [I,C*]; C12N0005-08 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4   ANSWER 7 OF 8  USPATFULL on STN
AN      97:44927  USPATFULL
TI      Method for culturing Chinese hamster ovary cells
IN      Keen, Michael J., Beckenham, England
        Rapson, Nicholas T., Beckenham, England
PA      Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S.
        corporation)
PI      US 5633162              19970527
AI      US 1994-205379          19940304 (8)
RLI     Continuation of Ser. No. US 1992-991717, filed on 18 Dec 1992, now
        patented, Pat. No. US 5316938 which is a continuation of Ser. No. US
        1991-777729, filed on 16 Oct 1991, now abandoned
PRAI    GB 1990-22545       19901017
DT      Utility
FS      Granted
LN.CNT 700
INCL    INCLM: 435/384.000
        INCLS: 435/386.000; 435/387.000
NCL     NCLM:  435/384.000
        NCLS:  435/386.000; 435/387.000
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IC      [6]
        ICM    C12N005-00
        IPCI   C12N0005-00 [ICM,6]
        IPCR   C07K0016-18 [I,C*]; C07K0016-28 [I,A]; C12N0005-00 [I,C*];
               C12N0005-00 [I,A]
EXF     435/240.1; 435/240.3; 435/240.31

L4   ANSWER 8 OF 8  USPATFULL on STN
AN      94:46895  USPATFULL
TI      Defined media for serum-free tissue culture
IN      Keen, Michael J., Kent, England
        Rapson, Nicholas T., Kent, England
PA      Burroughs Wellcome Co., Research Triangle Park, NC, United States (U.S.
        corporation)
PI      US 5316938              19940531
AI      US 1992-991717          19921218 (7)
RLI     Continuation of Ser. No. US 1991-777729, filed on 16 Oct 1991, now
        abandoned
PRAI    GB 1990-22545       19901017
DT      Utility
FS      Granted
LN.CNT 608
INCL    INCLM: 435/240.310
        INCLS: 435/240.200; 435/240.250; 435/071.100
NCL     NCLM:  435/404.000
        NCLS:  435/071.100
IC      [5]
        ICM    C12N005-02
        IPCI   C12N0005-02 [ICM,5]
        IPCR   C07K0016-18 [I,C*]; C07K0016-28 [I,A]; C12N0005-00 [I,C*];
               C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
               C12N0009-72 [I,C*]; C12N0009-72 [I,A]
EXF     435/240.31; 435/240.2


=> d l4 8 ab

L4   ANSWER 8 OF 8  USPATFULL on STN
AB      A biochemically defined culture medium for culturing
        engineered Chinese hamster ovary (CHO) cell lines, which is essentially
        free from protein, lipid and carbohydrate isolated from an animal
        source, comprising water, an osmolality regulator, a buffer, an energy
        source, amino acids including L-glutamine, an inorganic or recombinant
        iron source, and a synthetic or recombinant growth factor, and
        optionally non-ferrous metal ions vitamins and cofactors; also cells
        adapted to grow in such a culture medium.


=> d l4 8 kwic

L4   ANSWER 8 OF 8  USPATFULL on STN
TI      Defined media for serum-free tissue culture
AB      A biochemically defined culture medium for culturing
        engineered Chinese hamster ovary (CHO) cell lines, which is essentially
        free from protein, lipid and carbohydrate isolated from.  .  .  or
        recombinant growth factor, and optionally non-ferrous metal ions
        vitamins and cofactors; also cells adapted to grow in such a
        culture medium.
SUMM    The present invention relates to a biochemically defined culture
        medium for culturing Chinese hamster ovary (CHO) cell lines and
        cells adapted to grow in the culture medium.
SUMM    .  .  .  which a CHO cell line is transfected with a product gene and a
```

selectable marker gene) are routinely grown in culture media containing serum. (References: J. Mol. App. Gen. 1981, 1, 165-175; Mol. & Cell Biol. 5, 1750-1759, 1985; PNAS 80 pp. . . and Cellular Biology 4, 166-172, 1984). Fetal bovine serum (FBS) is probably the most extensively utilised serum for mammalian cell culture , although other mammalian sera are used. However, the use of serum poses a number of problems. Serum is an expensive. . .

SUMM Furthermore, the presence of animal proteins in culture media can require lengthy purification procedures, in particular the presence of bovine antibodies in bovine serum albumin (BSA) makes purification of the desired antibodies expressed by the recombinant CHO cell line, extremely difficult. Removal of bovine antibody from the medium prior to use is possible but this and the additional product testing required, adds greatly to the overall cost of production of the product. Consequently, there has been much research into finding a culture medium devoid of animal components which will support cellular growth, especially of CHO cells. Unfortunately, the problems associated with the provision of such a medium are themselves numerous. CHO cells do not readily grow in serum-free conditions. In addition, the removal of serum may also. . .

SUMM A culture medium which is serum-free but not free from animal components is described by Mendiaz et al (In Vitro Cellular & Development Biology Vol. 22, No. 2, 1986) for use in the culture of CHO K1 cells. The medium is a modification of the medium developed by Ham (Microbiology 53 1965 288-293) which is known as "Ham's F12". Other examples of media have been based on Ham's F12 medium for example as disclosed in EPA390327 and EP325190. These media contain transferrin as the serum substitute, but transferrin is derived from an animal source, so the resulting media do not overcome the contamination problems associated with the use of serum.

SUMM The present invention therefore provides a biochemically defined culture medium for culturing engineered CHO cells which is essentially free from protein, lipid and carbohydrate isolated from an animal source, comprising. . .

SUMM The components of the medium are mostly inorganic, synthetic or recombinant and as such are not obtained directly from any animal source. Some components may. . . to the cells used to produce the components. Further purification steps may be employed to remove cell proteins. Thus, a medium which is essentially free from all protein, lipid and carbohydrate isolated from an animal source, can be achieved. The preferred culture medium of the invention contains no protein, lipid and carbohydrate isolated from an animal source.

SUMM Medium A as set out in Table 1, is an example of a medium which provides the preferred quantities of water, osmolality regulator, buffer, energy source, amino acids, non-ferrous metal ions, vitamins and co-factors as a basis for a culture medium according to the invention. This medium does not contain any hypoxanthine or thymidine and is commercially available from GIBCO Ltd., Unit 4, Cowley Mill Td. Est., Uxbridge UB8 2YG. It is similar to a published culture medium (Iscoves and Melcher (1978) J. Exp. Med. 1. 47,923) but does not contain any bovine serum albumin, pure human transferrin. . .

SUMM . . . any iron source may be used which is not isolated from an animal source, for example, chemical iron chelators or recombinant protein iron carriers.

SUMM Serum-free media disclosed to date contain hypoxanthine or thymidine. This could bypass the selection pressure placed on the dhfr selection and amplification. . . genetic material specifying the product and the dhfr genes. Therefore, in another aspect of the invention there is provided a culture medium for the growth of engineered dhfr.sup.- CHO cells in accordance with the invention, essentially free from hypoxanthine and/or thymidine.

SUMM The culture medium of the present invention supports CHO cell growth and when supplemented with an appropriate agent such as methotrexate for the. . . hypoxanthine and thymidine at concentrations which are insufficient to bypass selection of the dhfr system may be present in the medium, but the presence of these two nucleotide precursors is not preferred for use with the present invention.

SUMM . . . To minimise the occurrence of cellular damage it is advantageous for the medium to contain a cell protectant such as polyethylene glycol, polyvinyl alcohols or pluronic polyols. Of these, PLURONIC (polyol, BASF Wyandotte Corp) polyol F68 is preferred since unlike polyvinyl alcohols. . .

SUMM The media of the invention for culturing recombinant CHO cells are capable of supporting the growth and secretion of product from such cells in suspension in small and large scale fermenters, static cultures and/or spinners. The culture medium according to the invention is also capable of supporting growth of cells at high cell density namely greater than 1+10.sup.5. . . up to or greater than 1.5+10.sup.6 cells/ml and product secretion of 30 mg/l up to greater than 150 mg/l. The medium according to the invention is also capable of supporting this growth and product secretion over multiple passages lasting upto or. . .

SUMM In a further aspect of the invention there is provided an engineered CHO cell adapted to grow in a medium according to the invention. In particular a CHO cell engineered to express proteins such as tissue plasminogen activator or antibodies. . . transfected with a gene encoding a biologically active protein and a dhfr selectable marker gene, adapted to grow in a culture medium according to the invention. The protein is preferably an antibody as defined above.

SUMM The ingredients of the culture medium may be added in any order but it is preferable to add the iron source and when used, tyrosine, last. . .

DETD . . . with trypsin/versene, washed in Iscoves medium without supplements, centrifuged and resuspended at 5+10.sup.4 /ml in WCM4 medium +0.25% peptone +0.1% polyethylene glycol (PEG) 10,000+0.5% fetal bovine serum (FBS) without methotrexate (MTX). Three 25 cm.sup.2 flasks were set up with 10 ml of cell. . .

DETD After six days, the flasks were pooled and added to an equal volume of WCM4+MTX without peptone or PEG, and were transferred to a 75 cm.sup.2 flask.

DETD . . . pH control to 7-7.2. The fermenter was seeded on day 0 with 0.22+10.sup.6 cells/ml in WCM4 (Example 1) with 0.1% polyethylene glycol (PEG) 10,000 and 0.25% soy peptone, and was top gassed with O.sub.2. The cells were routinely passaged using fresh medium and. . .

DETD On day 50 onwards WCM5 (Example 2) was used together with peptone and PEG instead of WCM4.

DETD On day 53 the PEG was replaced with 0.1% PLURONIC F68. The resulting growth and antibody levels achieved are shown the the attached graphs (FIGS.. . .

DETD . . . engineered to produce tPA under methotrexate selection. This cell line had been routinely grown in a fermenter as a suspension culture using normal growth medium consisting of RPMI 1640 medium (GIBCO), 2.5% acid hydrolysed adult bovine serum (Imperial), 0.5% Tryptone, 50 IU/ml polymycin, 20 IU/ml neomycin, 500 nM methotrexate (MTX).

DETD 46B 0.25%w/v N-Z Soy Peptone (Sigma P1265), 0.1%w/v Polyethylene

```
       glycol (PEG) 20,000 (Serva, CARBOWAX 20M), 1 uM MTX.
DETD   46C 0.25%w/v Yeast extract (Sigma Y0500), 0.1%w/v PEG 20,000 1
       um MTX. In this medium the Iscoves' in CM4 was replaced by RPMI 1640
       medium (ICN FLOW).
DETD   46D 0.25%w/v Yeast extract, 0.1%w/v PEG 20,000, 1 um MTX.
DETD   46E 0.25%w/v Yeast extract, 0.1%w/v PEG 20,000, 0.25% Foetal
       bovine serum (Imperial), 1 uM MTX.
DETD   The yeast extract, Peptone and PEG were made up as 10% w/v
       solutions with water (Wellcome media production unit) and filtered
       through a 0.2 um disposable.  .  .
DETD   The specific activity of supernatants from different pass levels of
       cells grown in WCM4 with peptone and 0.1% PEG 20K were
       measured by a combination of ELISA and clot lysis assay. The specific
       activities of different cell passages are.  .  .
CLM    What is claimed is:
       1. A culture medium which comprises: a base
       medium containing the amino acids, non-ferrous metal ions,
       vitamins, and cofactors essentially as set forth in Table I; an
       osmolality of the medium within the range of about 200-350
       mOsm; at least one buffer selected from CaCl.sub.2.2H.sub.2 O,
       MgSO.sub.4.7H.sub.2 O, NaH.sub.2 PO.sub.4.2H.sub.2 O, sodium pyruvate,
       HEPES, and MOPS in an amount sufficient to maintain the medium
       within the pH range of 6.5-7.5; about 1000-10,000 mg of mannose,
       fructose, glucose, or maltose;; about 5 ml of 200.  .  .  about 0.01-1.0
       mg of putrescine; about 5 μg-5 mg of recombinant insulin; and
       sufficient water to comprise one liter of medium; provided
       that said medium is essentially free of proteins,
       carbohydrates, and lipids isolated from animal sources.



=> d hist

     (FILE 'HOME' ENTERED AT 23:19:10 ON 28 MAR 2008)

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
     AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 23:19:26 ON 28 MAR 2008
                SEA (TRANSFERRIN OR INSULIN)(P)SUBSTITUTE? AND (PEG OR POLYETHY
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                0*  FILE ADISNEWS
                0*  FILE ANTE
                0*  FILE AQUALINE
                0*  FILE BIOENG
               10*  FILE BIOTECHABS
               10*  FILE BIOTECHDS
                0*  FILE BIOTECHNO
                5   FILE CAPLUS
                0*  FILE CEABA-VTB
                0*  FILE CIN
                1   FILE EMBASE
                1*  FILE ESBIOBASE
                0*  FILE FOMAD
                0*  FILE FOREGE
                0*  FILE FROSTI
                0*  FILE FSTA
                2   FILE IFIPAT
                0*  FILE KOSMET
                1   FILE MEDLINE
                0*  FILE NTIS
                0*  FILE NUTRACEUT
               1*  FILE PASCAL
               0*  FILE PHARMAML
               1   FILE PHIN
               1   FILE SCISEARCH
             484   FILE USPATFULL
              82   FILE USPAT2
               0*  FILE WATER
               5   FILE WPIDS
               5   FILE WPINDEX
L1              QUE (TRANSFERRIN OR INSULIN)(P) SUBSTITUTE? AND (PEG OR POLYETH
               ---------

     FILE 'BIOTECHDS, CAPLUS, EMBASE, ESBIOBASE, IFIPAT, MEDLINE, PASCAL,
     PHIN, SCISEARCH, USPATFULL, USPAT2' ENTERED AT 23:22:11 ON 28 MAR 2008
L2          589 S L1
L3          132 S L2 AND RECOMBINANT PROTEIN?
L4            8 S L3 AND ANIMAL PROTEIN?
L5            3 S L3 AND SODIUM ERYTHORBATE

=> s l4 and substitute(p)transferrin
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'SUBSTITUTE(P)TRANSFERRI'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'SUBSTITUTE(P)TRANSFERRI'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'SUBSTITUTE(P)TRANSFERRI'
L6            8 L4 AND SUBSTITUTE(P) TRANSFERRIN

=> d l6 1-8

L6    ANSWER 1 OF 8  BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
AN    2004-15746  BIOTECHDS
TI    Animal protein free composition for culturing cells
      or tissues comprises polyethylene glycol as an
      albumin substitute;
           animal protein-free composition for use in tissue
         culture and gene therapy
AU    HERON A
PA    MACO PHARMA SA
PI    EP 1411115 21 Apr 2004
AI    EP 2003-292374 26 Sep 2003
PRAI  FR 2002-12878 16 Oct 2002; FR 2002-12878 16 Oct 2002
DT    Patent
LA    French

L6   ANSWER 2 OF 8  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2004:326209  CAPLUS
DN   140:317692
TI   Animal cell culture or tissue culture media
     containing polyethylene glycol
IN   Heron, Antoine
PA   Maco Pharma, Fr.
SO   Eur. Pat. Appl., 11 pp.
     CODEN: EPXXDW
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   EP 1411115           A1    20040421    EP 2003-292374         20030926
     EP 1411115           B1    20070509
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     FR 2846004           A1    20040423    FR 2002-12878          20021016
     FR 2846004           B1    20060623
     AT 361971            T     20070615    AT 2003-292374         20030926
     AU 2003252890        A1    20040506    AU 2003-252890         20031009
     CA 2444468           A1    20040416    CA 2003-2444468        20031015
     US 2004087021        A1    20040506    US 2003-685609         20031015
     JP 2004135672        A     20040513    JP 2003-356717         20031016
PRAI FR 2002-12878        A     20021016
RE.CNT  4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 3 OF 8  IFIPAT  COPYRIGHT 2008 IFI on STN
AN    10579799  IFIPAT;IFIUDB;IFICDB
TI    COMPOSITON FOR CULTURING CELLS, IN PARTICULAR ANIMAL OR TISSUE CELLS, AND
      A CULTURE MEDIUM COMPRISIING SUCH A COMPOSITION;
      NUTRIENT BROTH COMPRISING SODIUM ERYTHORBATE FOR PROPAGATING EUKARYOTIC
      CELLS; BIOREACTORS AND HETEROLOGOUS PROTEIN EXPRESSION
IN    Heron Antoine (FR)
PA    Unassigned Or Assigned To Individual (68000)
PPA   Macopharma FR (Probable)
PI    US 2004087021   A1  20040506
AI    US 2003-685609      20031015
PRAI  FR 2002-12878       20021016
FI    US 2004087021       20040506
DT    Utility; Patent Application - First Publication
FS    CHEMICAL
      APPLICATION
ED    Entered STN: 7 May 2004
      Last Updated on STN: 31 Oct 2005
CLMN  38

L6   ANSWER 4 OF 8  USPATFULL on STN
AN     2007:220488  USPATFULL
TI     Method for culturing Chinese hamster ovary cells
IN     Keen, Michael J., Beckenham, UNITED KINGDOM
       Rapson, Nicholas T., Stapleford, UNITED KINGDOM
PA     SmithKline Beecham Corporation, Philadelphia, PA, UNITED STATES (U.S.
       corporation)
PI     US 39792            E1  20070821
       US 5633162              19970527 (Original)
AI     US 2004-995010          20041122 (10)
       US 1994-205379          19940304 (Original)
RLI    Continuation of Ser. No. US 1992-991717, filed on 18 Dec 1992, Pat. No.
       US 5316938 Continuation of Ser. No. US 1991-777729, filed on 16 Oct
       1991, ABANDONED
PRAI   GB 1990-22545       19901017
DT     Reissue
FS     GRANTED
LN.CNT 983
INCL   INCLM: 435/384.000
       INCLS: 435/386.000; 435/387.000; 435/325.000; 435/358.000; 435/359.000;
              435/360.000; 435/361.000; 435/383.000; 435/326.000
NCL    NCLM:  435/384.000
       NCLS:  435/325.000; 435/326.000; 435/358.000; 435/359.000; 435/360.000;
              435/361.000; 435/383.000; 435/386.000; 435/387.000
IC     IPCI   C12N0005-00 [I,A]
EXF    435/325; 435/326; 435/358; 435/359; 435/360; 435/361; 435/362; 435/383;
       435/384; 435/387; 435/386

L6   ANSWER 5 OF 8  USPATFULL on STN
AN     2006:86590  USPATFULL
```

```
TI      Cell culture media
IN      Abitorabi, M. Abi, Morgan Hill, CA, UNITED STATES
        Guerini, Michael N., Ong, NE, UNITED STATES
        Taylor, Stephen A., Santa Cruz, CA, UNITED STATES
        Hernandez, Guadalupe G., San Jose, CA, UNITED STATES
        Simonsen, Christian C., Carmel, CA, UNITED STATES
PI      US 2006073591       A1  20060406
AI      US 2005-32558       A1  20050110 (11)
PRAI    US 2004-535580P     20040109 (60)
        US 2004-568084P     20040504 (60)
DT      Utility
FS      APPLICATION
LN.CNT 6174
INCL    INCLM: 435/404.000
        INCLS: 435/070.210
NCL     NCLM:  435/404.000
        NCLS:  435/070.210
IC      IPCI   C12P0021-04 [I,A]; C12N0005-00 [I,A]
        IPCR   C12P0021-04 [I,A]; C12N0005-00 [I,C]; C12N0005-00 [I,A];
               C12P0021-04 [I,C]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6   ANSWER 6 OF 8  USPATFULL on STN
AN      2004:114182  USPATFULL
TI      Compositon for culturing cells, in particular animal or tissue cells,
        and a culture medium comprisiing such a composition
IN      Heron, Antoine, Halluin, FRANCE
PI      US 2004087021       A1  20040506
AI      US 2003-685609      A1  20031015 (10)
PRAI    FR 2002-12878       20021016
DT      Utility
FS      APPLICATION
LN.CNT 619
INCL    INCLM: 435/404.000
NCL     NCLM:  435/404.000
IC      [7]
        ICM    C12N005-02
        IPCI   C12N0005-02 [ICM,7]
        IPCR   C12N0005-06 [I,C*]; C12N0005-06 [I,A]; C12N0005-00 [I,C*];
               C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
               C12N0005-08 [I,C*]; C12N0005-08 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6   ANSWER 7 OF 8  USPATFULL on STN
AN      97:44927  USPATFULL
TI      Method for culturing Chinese hamster ovary cells
IN      Keen, Michael J., Beckenham, England
        Rapson, Nicholas T., Beckenham, England
PA      Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S.
        corporation)
PI      US 5633162              19970527
AI      US 1994-205379          19940304 (8)
RLI     Continuation of Ser. No. US 1992-991717, filed on 18 Dec 1992, now
        patented, Pat. No. US 5316938 which is a continuation of Ser. No. US
        1991-777729, filed on 16 Oct 1991, now abandoned
PRAI    GB 1990-22545       19901017
DT      Utility
FS      Granted
LN.CNT 700
INCL    INCLM: 435/384.000
        INCLS: 435/386.000; 435/387.000
NCL     NCLM:  435/384.000
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       NCLS:  435/386.000; 435/387.000
IC     [6]
       ICM    C12N005-00
       IPCI   C12N0005-00 [ICM,6]
       IPCR   C07K0016-18 [I,C*]; C07K0016-28 [I,A]; C12N0005-00 [I,C*];
              C12N0005-00 [I,A]
EXF    435/240.1; 435/240.3; 435/240.31

L6   ANSWER 8 OF 8  USPATFULL on STN
AN     94:46895  USPATFULL
TI     Defined media for serum-free tissue culture
IN     Keen, Michael J., Kent, England
       Rapson, Nicholas T., Kent, England
PA     Burroughs Wellcome Co., Research Triangle Park, NC, United States (U.S.
       corporation)
PI     US 5316938              19940531
AI     US 1992-991717          19921218 (7)
RLI    Continuation of Ser. No. US 1991-777729, filed on 16 Oct 1991, now
       abandoned
PRAI   GB 1990-22545       19901017
DT     Utility
FS     Granted
LN.CNT 608
INCL   INCLM: 435/240.310
       INCLS: 435/240.200; 435/240.250; 435/071.100
NCL    NCLM:  435/404.000
       NCLS:  435/071.100
IC     [5]
       ICM    C12N005-02
       IPCI   C12N0005-02 [ICM,5]
       IPCR   C07K0016-18 [I,C*]; C07K0016-28 [I,A]; C12N0005-00 [I,C*];
              C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
              C12N0009-72 [I,C*]; C12N0009-72 [I,A]
EXF    435/240.31; 435/240.2


=> d l4 4-8

L4   ANSWER 4 OF 8  USPATFULL on STN
AN     2007:220488  USPATFULL
TI     Method for culturing Chinese hamster ovary cells
IN     Keen, Michael J., Beckenham, UNITED KINGDOM
       Rapson, Nicholas T., Stapleford, UNITED KINGDOM
PA     SmithKline Beecham Corporation, Philadelphia, PA, UNITED STATES (U.S.
       corporation)
PI     US 39792            E1  20070821
       US 5633162              19970527 (Original)
AI     US 2004-995010          20041122 (10)
       US 1994-205379          19940304 (Original)
RLI    Continuation of Ser. No. US 1992-991717, filed on 18 Dec 1992, Pat. No.
       US 5316938 Continuation of Ser. No. US 1991-777729, filed on 16 Oct
       1991, ABANDONED
PRAI   GB 1990-22545       19901017
DT     Reissue
FS     GRANTED
LN.CNT 983
INCL   INCLM: 435/384.000
       INCLS: 435/386.000; 435/387.000; 435/325.000; 435/358.000; 435/359.000;
              435/360.000; 435/361.000; 435/383.000; 435/326.000
NCL    NCLM:  435/384.000
       NCLS:  435/325.000; 435/326.000; 435/358.000; 435/359.000; 435/360.000;
              435/361.000; 435/383.000; 435/386.000; 435/387.000
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IC      IPCI   C12N0005-00 [I,A]
EXF     435/325; 435/326; 435/358; 435/359; 435/360; 435/361; 435/362; 435/383;
        435/384; 435/387; 435/386

L4   ANSWER 5 OF 8  USPATFULL on STN
AN      2006:86590  USPATFULL
TI      Cell culture media
IN      Abitorabi, M. Abi, Morgan Hill, CA, UNITED STATES
        Guerini, Michael N., Ong, NE, UNITED STATES
        Taylor, Stephen A., Santa Cruz, CA, UNITED STATES
        Hernandez, Guadalupe G., San Jose, CA, UNITED STATES
        Simonsen, Christian C., Carmel, CA, UNITED STATES
PI      US 2006073591       A1  20060406
AI      US 2005-32558       A1  20050110 (11)
PRAI    US 2004-535580P     20040109 (60)
        US 2004-568084P     20040504 (60)
DT      Utility
FS      APPLICATION
LN.CNT 6174
INCL    INCLM: 435/404.000
        INCLS: 435/070.210
NCL     NCLM:  435/404.000
        NCLS:  435/070.210
IC      IPCI   C12P0021-04 [I,A]; C12N0005-00 [I,A]
        IPCR   C12P0021-04 [I,A]; C12N0005-00 [I,C]; C12N0005-00 [I,A];
               C12P0021-04 [I,C]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4   ANSWER 6 OF 8  USPATFULL on STN
AN      2004:114182  USPATFULL
TI      Compositon for culturing cells, in particular animal or tissue cells,
        and a culture medium comprisiing such a composition
IN      Heron, Antoine, Halluin, FRANCE
PI      US 2004087021       A1  20040506
AI      US 2003-685609      A1  20031015 (10)
PRAI    FR 2002-12878       20021016
DT      Utility
FS      APPLICATION
LN.CNT 619
INCL    INCLM: 435/404.000
NCL     NCLM:  435/404.000
IC      [7]
        ICM    C12N005-02
        IPCI   C12N0005-02 [ICM,7]
        IPCR   C12N0005-06 [I,C*]; C12N0005-06 [I,A]; C12N0005-00 [I,C*];
               C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
               C12N0005-08 [I,C*]; C12N0005-08 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4   ANSWER 7 OF 8  USPATFULL on STN
AN      97:44927  USPATFULL
TI      Method for culturing Chinese hamster ovary cells
IN      Keen, Michael J., Beckenham, England
        Rapson, Nicholas T., Beckenham, England
PA      Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S.
        corporation)
PI      US 5633162              19970527
AI      US 1994-205379          19940304 (8)
RLI     Continuation of Ser. No. US 1992-991717, filed on 18 Dec 1992, now
        patented, Pat. No. US 5316938 which is a continuation of Ser. No. US
        1991-777729, filed on 16 Oct 1991, now abandoned
PRAI    GB 1990-22545       19901017
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DT     Utility
FS     Granted
LN.CNT 700
INCL   INCLM: 435/384.000
       INCLS: 435/386.000; 435/387.000
NCL    NCLM:  435/384.000
       NCLS:  435/386.000; 435/387.000
IC     [6]
       ICM    C12N005-00
       IPCI   C12N0005-00 [ICM,6]
       IPCR   C07K0016-18 [I,C*]; C07K0016-28 [I,A]; C12N0005-00 [I,C*];
              C12N0005-00 [I,A]
EXF    435/240.1; 435/240.3; 435/240.31

L4   ANSWER 8 OF 8  USPATFULL on STN
AN     94:46895  USPATFULL
TI     Defined media for serum-free tissue culture
IN     Keen, Michael J., Kent, England
       Rapson, Nicholas T., Kent, England
PA     Burroughs Wellcome Co., Research Triangle Park, NC, United States (U.S.
       corporation)
PI     US 5316938              19940531
AI     US 1992-991717          19921218 (7)
RLI    Continuation of Ser. No. US 1991-777729, filed on 16 Oct 1991, now
       abandoned
PRAI   GB 1990-22545       19901017
DT     Utility
FS     Granted
LN.CNT 608
INCL   INCLM: 435/240.310
       INCLS: 435/240.200; 435/240.250; 435/071.100
NCL    NCLM:  435/404.000
       NCLS:  435/071.100
IC     [5]
       ICM    C12N005-02
       IPCI   C12N0005-02 [ICM,5]
       IPCR   C07K0016-18 [I,C*]; C07K0016-28 [I,A]; C12N0005-00 [I,C*];
              C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
              C12N0009-72 [I,C*]; C12N0009-72 [I,A]
EXF    435/240.31; 435/240.2


=> d l4 4 ab

L4   ANSWER 4 OF 8  USPATFULL on STN
AB       A biochemically defined culture medium for culturing
       engineered Chinese hamster ovary (CHO) cell lines, which is essentially
       free from protein, lipid and carbohydrate isolated from an animal
       source, having water, an osmolality regulator, a buffer, an energy
       source, amino acids including L-glutamine, an inorganic or recombinant
       iron source, and a synthetic or recombinant growth factor, and
       optionally non-ferrous metal ions vitamins and cofactors. Also cells
       adapted to grow in such a culture medium.

       REEXAMINATION RESULTS

       The questions raised in reexamination request number 90/006656, filed Jun.
       2, 2003 have been considered and the results thereof are reflected in
       this reissue patent which constitutes the reexamination certificate
       required by 35 U.S.C. 307 as provided in 37 CFR 1.570(e), for ex parte
       reexaminations, or the reexamination certificate required by 35 U.S.C.
       316 as provided in 37 CFR 1.997(e) for inter partes reexaminations.
```

```
=> d l4 4 kwic

L4   ANSWER 4 OF 8  USPATFULL on STN
AB      A biochemically defined culture medium for culturing
        engineered Chinese hamster ovary (CHO) cell lines, which is essentially
        free from protein, lipid and carbohydrate isolated from.  .  .  or
        recombinant growth factor, and optionally non-ferrous metal ions
        vitamins and cofactors. Also cells adapted to grow in such a
        culture medium.
SUMM    The present invention relates to a biochemically defined culture
        medium for culturing Chinese hamster ovary (CHO) cell lines and
        cells adapted to grow in the culture medium.
SUMM    .  .  .  which a CHO cell line is transfected with a product gene and a
        selectable marker gene) are routinely grown in culture
        media containing serum. (References: J. Mol. App. Gen. 1981, 1,
        165-175; Mol. & Cell Biol. 5, 1750-1759, 1985; PNAS 80 pp.  .  .  and
        Cellular Biology 4, 166-172, 1984). Fetal bovine serum (FBS) is probably
        the most extensively utilised serum for mammalian cell culture
        , although other mammalian sera are used. However, the use of serum
        poses a number of problems. Serum is an expensive.  .  .  to require the
        sourcing of bovine products from those areas which are free from (BSE)
        infections. Furthermore, the presence of animal
        proteins in culture media can require
        lengthy purification procedures, in particular the presence of bovine
        antibodies in bovine serum albumin (BSA) makes purification of the
        desired antibodies expressed by the recombinant CHO cell line, extremely
        difficult. Removal of bovine antibody from the medium prior to
        use is possible but this and the additional product testing required,
        adds greatly to the ( everall )  overall cost of production of the
        product. Consequently, there has been much research into finding a
        culture medium devoid of animal components which will
        support cellular growth, especially of CHO cells. Unfortunately, the
        problems associated with the provision of such a medium are
        themselves numerous. CHO cells do not readily grow in serum-free
        conditions. In addition, the removal of serum may also.  .  .
SUMM    A culture medium which is serum-free but not free
        from animal components is described by Mendiaz et al (In Vitro Cellular
        & Development Biology Vol.22, No.2, 1986) for use in the culture
        of CHO K1 cells. The medium is a modification of the
        medium developed by Ham (Microbiology 53 1965 288-293) which is
        known as "Ham's F12". Other examples of media have been based
        on Ham's F12 medium for example as disclosed in EPA390327 and
        EP325190. These media contain transferrin as the
        serum substitute, but transferrin is derived from an
        animal source, so the resulting media do not overcome the
        contamination problems associated with the use of serum.
SUMM    The present invention therefore provides a biochemically defined
        culture medium for culturing engineered CHO cells
        which is essentially free from protein, lipid and carbohydrate isolated
        from an animal source, comprising.  .  .
SUMM    The components of the medium are mostly inorganic, synthetic
        or recombinant and as such are not obtained directly from any animal
        source. Some components may.  .  .  to the cells used to produce the
        components. Further purification steps may be employed to remove cell
        proteins. Thus, a medium which is essentially free from all
        protein, lipid and carbohydrate isolated from an animal source, can be
        achieved. The preferred culture medium of the
        invention contains no protein, lipid and carbohydrate isolated from an
        animal source.
SUMM    Medium A as set out in Table 1, is an example of a
```

medium which provides the preferred quantities of water, osmolality regulator, buffer, energy source, amino acids, non-ferrous metal ions, vitamins and co-factors as a basis for a culture medium according to the invention. This medium does not contain any hypoxanthine or thymidine and is commercially available from GIBCO Ltd., Unit 4, Cowley Mill Td. Est., Uxbridge UB8 2YG. It is similar to a published culture medium (Iscoves and Melcher (1978) J. Exp. Med. 1, 47,923) but does not contain any bovine serum albumin, pure human transferrin. . .

SUMM . . . any iron source may be used which is not isolated from an animal source, for example, chemical iron chelators or recombinant protein iron carriers.

SUMM Serum-free media disclosed to date contain hypoxanthine or thymidine. This could bypass the selection pressure placed on the dhfr selection and amplification. . . genetic material specifying the product and the dhfr genes. Therefore, In another aspect of the invention there is provided a culture medium for the growth of engineered dhfr.sup.- CHO cells in accordance with the invention, essentially free from hypoxanthine and/or thymidine.

SUMM The culture medium of the present invention supports CHO cell growth and when supplemented with an appropriate agent such as methotrexate for the. . . hypoxanthine and thymidine at concentrations which are insufficient to bypass selection of the dhfr system may be present in the medium, but the presence of these two nucleotide precursors is not preferred for use with the present invention.

SUMM . . . To minimise the occurrence of cellular damage it is advantageous for the medium to contain a cell protectant such as polyethylene glycol, polyvinyl alcohols or pluronic polyols. Of these, Pluronic® (polyol, BASF Wyandotte Corp.) polyol F68 is preferred since unlike polyvinyl alcohols. . .

SUMM The media of the invention for culturing recombinant CHO cells are capable of supporting the growth and secretion of product from such cells in suspension in small and large scale (fermenters) fermentors, static cultures and/or spinners. The culture medium according to the invention is also capable of supporting growth of cells at high cell density namely greater than 1+10.sup.5. . . up to or greater than 1.5+10.sup.6 cells/ml and product secretion of 30 mg/l up to greater than 150 mg/l. The medium according to the invention is also capable of supporting this growth and product secretion over multiple passages lasting up to. . .

SUMM In a further aspect of the invention there is provided an engineered CHO cell adapted to grow in a medium according to the invention. In particular a CHO cell engineered to express proteins such as tissue plasminogen activator or antibodies. . . transfected with a gene encoding a biologically active protein and a dhfr selectable marker gene, adapted to grow in a culture medium according to the invention. The protein is preferably an antibody as defined above.

SUMM The ingredients of the culture medium may be added in any order but it is preferable to add the iron source and when used, tyrosine, last. . .

DETD . . . from the plastic with trypsin/versene, washed in Iscoves medium without supplements, centrifuged and resuspended at 5+10.sup.4/ml in WCM4 medium+0.25% peptone+0.1% polyethylene glycol (PEG) 10,000+0.5% fetal bovine serum (FBS) without methotrexate (MTX). Three 25 cm.sup.2 flasks were set up with 10 ml of cell. . .

DETD After six days, the flasks were pooled and added to an equal volume of WCM4+MTX without peptone or PEG, and were transferred to a 75 cm.sup.2 flask.

DETD . . . 7-7.2. The (fermenter) fermentor was seeded on day 0 with

```
       0.22+10.sup.6 cells/ml in WCM4 (Example 1) with 0.1%
       polyethylene glycol (PEG) 10,000 and 0.25%
       soy peptone, and was top gassed with O.sub.2. The cells were routinely
       passaged using fresh medium and.  .  .
DETD   On day 50 onwards WCM5 (Example 2) was used together with peptone and
       PEG instead of WCM4.
DETD   On day 53 the PEG was replaced with 0.1% Pluronic F68. The
       resulting growth and antibody levels achieved are shown the ( the )
       attached.  .  .
DETD   .  .  .  tPA under methotrexate selection. This cell line had been
       routinely grown in a ( fermenter )  fermentor as a suspension
       culture using normal growth medium consisting of RPMI
       1640 medium (GIBCO), 2.5% acid hydrolysed adult bovine serum
       (Imperial), 0.5% Tryptone, 50 IU/ml polymycin, 20 IU/ml neomycin, 500 nM
       methotrexate (MTX).
DETD   Medium WCM4 was formulated to which was added:

46B 0.25% w/v N-Z Soy Peptone (Sigma P1265), 0.1% w/v Polyethylene
       glycol (PEG) 20,000 (Serva, Carbowax® 20M), 1
       μM MTX.
46C 0.25% w/v Yeast extract (Sigma Y0500), 0.1% w/v PEG 20,000 1
       μM MTX. In this medium the Iscoves' in CM4 was replaced by RPMI 1640
       medium (ICN FLOW).
46D 0.25% w/v Yeast extract, 0.1% w/v PEG 20,000, 1 μM MTX.
46E 0.25% w/v Yeast extract, 0.1% w/v PEG 20,000, 0.25% Fetal bovine
       serum (Imperial), 1 μM MTX.
DETD   The yeast extract, Peptone and PEG were made up as 10% w/v
       solutions with water (Wellcome media production unit) and filtered
       through a 0.2 um disposable.  .  .
DETD   The specific activity of supernatants from differing pass levels of
       cells grown in WCM4 with peptone and 0.1% PEG 20K were
       measured by a combination of ELISA and clot lysis assay. The specific
       activities of different cell passages are.  .  .


=> s l4 and substitute transferrin
L7            0 L4 AND SUBSTITUTE TRANSFERRIN

=> s l4 and transferrin substitute
L8            4 L4 AND TRANSFERRIN SUBSTITUTE

=> d l8 1-4

L8   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2004:326209  CAPLUS
DN   140:317692
TI   Animal cell culture or tissue culture media
     containing polyethylene glycol
IN   Heron, Antoine
PA   Maco Pharma, Fr.
SO   Eur. Pat. Appl., 11 pp.
     CODEN: EPXXDW
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI   EP 1411115           A1    20040421    EP 2003-292374         20030926
     EP 1411115           B1    20070509
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     FR 2846004           A1    20040423    FR 2002-12878          20021016
     FR 2846004          B1    20060623
     AT 361971           T     20070615    AT 2003-292374        20030926
     AU 2003252890       A1    20040506    AU 2003-252890        20031009
     CA 2444468          A1    20040416    CA 2003-2444468       20031015
     US 2004087021       A1    20040506    US 2003-685609        20031015
     JP 2004135672       A     20040513    JP 2003-356717        20031016
PRAI FR 2002-12878       A     20021016
RE.CNT  4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8   ANSWER 2 OF 4  IFIPAT  COPYRIGHT 2008 IFI on STN
AN    10579799  IFIPAT;IFIUDB;IFICDB
TI    COMPOSITON FOR CULTURING CELLS, IN PARTICULAR ANIMAL OR TISSUE CELLS, AND
      A CULTURE MEDIUM COMPRISIING SUCH A COMPOSITION;
      NUTRIENT BROTH COMPRISING SODIUM ERYTHORBATE FOR PROPAGATING EUKARYOTIC
      CELLS; BIOREACTORS AND HETEROLOGOUS PROTEIN EXPRESSION
IN    Heron Antoine (FR)
PA    Unassigned Or Assigned To Individual (68000)
PPA   Macopharma FR (Probable)
PI    US 2004087021   A1  20040506
AI    US 2003-685609      20031015
PRAI  FR 2002-12878       20021016
FI    US 2004087021       20040506
DT    Utility; Patent Application - First Publication
FS    CHEMICAL
      APPLICATION
ED    Entered STN: 7 May 2004
      Last Updated on STN: 31 Oct 2005
CLMN  38

L8   ANSWER 3 OF 4  USPATFULL on STN
AN     2006:86590  USPATFULL
TI     Cell culture media
IN     Abitorabi, M. Abi, Morgan Hill, CA, UNITED STATES
       Guerini, Michael N., Ong, NE, UNITED STATES
       Taylor, Stephen A., Santa Cruz, CA, UNITED STATES
       Hernandez, Guadalupe G., San Jose, CA, UNITED STATES
       Simonsen, Christian C., Carmel, CA, UNITED STATES
PI     US 2006073591       A1  20060406
AI     US 2005-32558       A1  20050110 (11)
PRAI   US 2004-535580P     20040109 (60)
       US 2004-568084P     20040504 (60)
DT     Utility
FS     APPLICATION
LN.CNT 6174
INCL   INCLM: 435/404.000
       INCLS: 435/070.210
NCL    NCLM:  435/404.000
       NCLS:  435/070.210
IC     IPCI   C12P0021-04 [I,A]; C12N0005-00 [I,A]
       IPCR   C12P0021-04 [I,A]; C12N0005-00 [I,C]; C12N0005-00 [I,A];
              C12P0021-04 [I,C]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8   ANSWER 4 OF 4  USPATFULL on STN
AN     2004:114182  USPATFULL
TI     Compositon for culturing cells, in particular animal or tissue cells,
       and a culture medium comprisiing such a composition
IN     Heron, Antoine, Halluin, FRANCE
PI     US 2004087021       A1  20040506
AI     US 2003-685609      A1  20031015 (10)
PRAI   FR 2002-12878       20021016
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DT     Utility
FS     APPLICATION
LN.CNT 619
INCL   INCLM: 435/404.000
NCL    NCLM:  435/404.000
IC     [7]
       ICM    C12N005-02
       IPCI   C12N0005-02 [ICM,7]
       IPCR   C12N0005-06 [I,C*]; C12N0005-06 [I,A]; C12N0005-00 [I,C*];
              C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
              C12N0005-08 [I,C*]; C12N0005-08 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> s l4 and insulin substitute
L9            5 L4 AND INSULIN SUBSTITUTE

=> d l9 1-5

L9    ANSWER 1 OF 5  BIOTECHDS COPYRIGHT 2008 THE THOMSON CORP. on STN
AN    2004-15746  BIOTECHDS
TI    Animal protein free composition for culturing cells
      or tissues comprises polyethylene glycol as an
      albumin substitute;
          animal protein-free composition for use in tissue
        culture and gene therapy
AU    HERON A
PA    MACO PHARMA SA
PI    EP 1411115 21 Apr 2004
AI    EP 2003-292374 26 Sep 2003
PRAI  FR 2002-12878 16 Oct 2002; FR 2002-12878 16 Oct 2002
DT    Patent
LA    French

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       Taylor, Stephen A., Santa Cruz, CA, UNITED STATES
       Hernandez, Guadalupe G., San Jose, CA, UNITED STATES
       Simonsen, Christian C., Carmel, CA, UNITED STATES
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AI     US 2005-32558       A1  20050110 (11)
PRAI   US 2004-535580P     20040109 (60)
       US 2004-568084P     20040504 (60)
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DT     Utility
FS     APPLICATION
LN.CNT 619
INCL   INCLM: 435/404.000
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IC     [7]
       ICM    C12N005-02
       IPCI   C12N0005-02 [ICM,7]
       IPCR   C12N0005-06 [I,C*]; C12N0005-06 [I,A]; C12N0005-00 [I,C*];
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              C12N0005-00 [I,A]; C12N0005-02 [I,C*]; C12N0005-02 [I,A];
              C12N0005-08 [I,C*]; C12N0005-08 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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     (FILE 'HOME' ENTERED AT 23:19:10 ON 28 MAR 2008)

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     AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
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               5   FILE CAPLUS
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               1   FILE EMBASE
               1*  FILE ESBIOBASE
               0*  FILE FOMAD
               0*  FILE FOREGE
               0*  FILE FROSTI
               0*  FILE FSTA
               2   FILE IFIPAT
               0*  FILE KOSMET
               1   FILE MEDLINE
               0*  FILE NTIS
               0*  FILE NUTRACEUT
               1*  FILE PASCAL
               0*  FILE PHARMAML
               1   FILE PHIN
               1   FILE SCISEARCH
             484   FILE USPATFULL
              82   FILE USPAT2
               0*  FILE WATER
               5   FILE WPIDS
               5   FILE WPINDEX
L1              QUE (TRANSFERRIN OR INSULIN)(P) SUBSTITUTE? AND (PEG OR POLYETH
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     PHIN, SCISEARCH, USPATFULL, USPAT2' ENTERED AT 23:22:11 ON 28 MAR 2008
L2          589 S L1
L3          132 S L2 AND RECOMBINANT PROTEIN?
L4            8 S L3 AND ANIMAL PROTEIN?
L5            3 S L3 AND SODIUM ERYTHORBATE
L6            8 S L4 AND SUBSTITUTE(P)TRANSFERRIN
L7            0 S L4 AND SUBSTITUTE TRANSFERRIN
L8            4 S L4 AND TRANSFERRIN SUBSTITUTE
L9            5 S L4 AND INSULIN SUBSTITUTE

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STN INTERNATIONAL LOGOFF AT 23:29:41 ON 28 MAR 2008



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 NEWS  1          Web Page for STN Seminar Schedule - N. America
 NEWS  2  JUN 06  EPFULL enhanced with 260,000 English abstracts
 NEWS  3  JUN 06  KOREAPAT updated with 41,000 documents
 NEWS  4  JUN 13  USPATFULL and USPAT2 updated with 11-character
                  patent numbers for U.S. applications
 NEWS  5  JUN 19  CAS REGISTRY includes selected substances from
                  web-based collections
 NEWS  6  JUN 25  CA/CAplus and USPAT databases updated with IPC
                  reclassification data
 NEWS  7  JUN 30  AEROSPACE enhanced with more than 1 million U.S.
                  patent records
 NEWS  8  JUN 30  EMBASE, EMBAL, and LEMBASE updated with additional
                  options to display authors and affiliated
                  organizations
 NEWS  9  JUN 30  STN on the Web enhanced with new STN AnaVist
                  Assistant and BLAST plug-in
 NEWS 10  JUN 30  STN AnaVist enhanced with database content from EPFULL
 NEWS 11  JUL 28  CA/CAplus patent coverage enhanced
 NEWS 12  JUL 28  EPFULL enhanced with additional legal status
                  information from the epoline Register
 NEWS 13  JUL 28  IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
 NEWS 14  JUL 28  STN Viewer performance improved
 NEWS 15  AUG 01  INPADOCDB and INPAFAMDB coverage enhanced
 NEWS 16  AUG 13  CA/CAplus enhanced with printed Chemical Abstracts
                  page images from 1967-1998
 NEWS 17  AUG 15  CAOLD to be discontinued on December 31, 2008
 NEWS 18  AUG 15  CAplus currency for Korean patents enhanced
 NEWS 19  AUG 27  CAS definition of basic patents expanded to ensure
                  comprehensive access to substance and sequence
                  information
 NEWS 20  SEP 18  Support for STN Express, Versions 6.01 and earlier,
                  to be discontinued
 NEWS 21  SEP 25  CA/CAplus current-awareness alert options enhanced
                  to accommodate supplemental CAS indexing of
                  exemplified prophetic substances
 NEWS 22  SEP 26  WPIDS, WPINDEX, and WPIX coverage of Chinese and
                  and Korean patents enhanced
 NEWS 23  SEP 29  IFICLS enhanced with new super search field
 NEWS 24  SEP 29  EMBASE and EMBAL enhanced with new search and
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                  display fields
 NEWS 25  SEP 30  CAS patent coverage enhanced to include exemplified
                  prophetic substances identified in new Japanese-
                  language patents
 NEWS 26  OCT 07  EPFULL enhanced with full implementation of EPC2000
 NEWS 27  OCT 07  Multiple databases enhanced for more flexible patent
                  number searching

 NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
              AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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FILE 'HOME' ENTERED AT 21:32:17 ON 12 OCT 2008

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                       0.21       0.21

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       AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
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       DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 21:32:33 ON 12 OCT 2008

69 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s albmumin and (polyethylene glycol or PEG) and recombinant(p)protein? and
insulin substitute and transferin substitute
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          0*  FILE BIOENG
          0*  FILE BIOTECHABS
          0*  FILE BIOTECHDS
          0*  FILE BIOTECHNO
  15 FILES SEARCHED...
          0*  FILE CEABA-VTB
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          0*  FILE KOSMET
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          0*  FILE NUTRACEUT
          0*  FILE PASCAL
  47 FILES SEARCHED...
          0*  FILE PHARMAML
  65 FILES SEARCHED...
          0*  FILE WATER

   0 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L1   QUE ALBMUMIN AND (POLYETHYLENE GLYCOL OR PEG) AND RECOMBINANT(P) PROTEIN?
         AND INSULIN SUBSTITUTE AND TRANSFERIN SUBSTITUTE

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LOGOFF? (Y)/N/HOLD:y
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STN INTERNATIONAL LOGOFF AT 21:37:14 ON 12 OCT 2008
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